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· 论 著 ·

## 术后辅助放疗对中晚期胃印戒细胞癌患者预后的影响：基于人群的回顾性研究

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**[摘要]** **目的** 探讨术后辅助放疗对中晚期胃印戒细胞癌患者预后的影响。**方法** 收集监测、流行病学与最终结果 (SEER) 数据库中 2004—2015 年 1 694 例中晚期胃印戒细胞癌患者的信息, 将患者分为术后放疗组与术后未放疗组。利用 Kaplan-Meier 法分析两组患者的生存情况, 采用 log-rank 检验和 Cox 回归进行生存分析与亚组分析。

**结果** Kaplan-Meier 生存曲线显示术后放疗组患者的预后较术后未放疗组患者好 ( $P < 0.05$ )。log-rank 单因素分析结果显示, 年龄、种族、婚姻状况、肿瘤 TNM 分期、T 分期、N 分期、肿瘤原发部位、肿瘤最大径及是否接受化疗和术后是否接受放疗是中晚期胃印戒细胞癌患者预后的影响因素 ( $P$  均  $< 0.01$ )。进一步多因素 Cox 回归分析显示年龄、T 分期、N 分期、肿瘤最大径、是否接受化疗及术后是否接受放疗是患者预后的独立影响因素 ( $P$  均  $< 0.01$ )。亚组分析结果显示除 N0 期患者 ( $P > 0.05$ ) 外, 年龄  $\leq 70$  岁与  $> 70$  岁、不同 T 分期、有淋巴结转移 (N1~N3 期)、肿瘤最大径  $\leq 5$  cm 与  $> 5$  cm、接受化疗与未接受化疗的患者均能从术后辅助放疗中获益 ( $P$  均  $< 0.01$ )。**结论** 对于行手术治疗的中晚期胃印戒细胞癌患者, 术后接受辅助放疗患者的预后较未接受放疗者好。

**[关键词]** 印戒细胞癌; 胃肿瘤; 辅助放疗; 生存分析; SEER 数据库

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### Prognostic impact of postoperative adjuvant radiotherapy on patients with advanced gastric signet ring cell carcinoma: a population-based retrospective study

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**[Abstract]** **Objective** To investigate the effect of postoperative adjuvant radiotherapy on the prognosis of patients with advanced gastric signet ring cell carcinoma. **Methods** The data of 1 694 patients with advanced gastric signet ring cell carcinoma were collected from the Surveillance, Epidemiology, and End Results (SEER) database between 2004 and 2015. The patients were divided into 2 groups, with or without postoperative radiotherapy. Kaplan-Meier method was used to analyze the survival of patients in the 2 groups. Log-rank test and Cox regression were used for survival analysis and subgroup analysis. **Results** Kaplan-Meier survival curves showed that the prognosis of patients with postoperative radiotherapy was better than that without postoperative radiotherapy group ( $P < 0.05$ ). Log-rank univariate analysis showed that age, race, marital status, TNM stage, T stage, N stage, primary tumor location, maximum tumor diameter, whether to receive chemotherapy or not and whether to receive postoperative radiotherapy or not were the prognostic factors for advanced gastric signet ring cell carcinoma patients (all  $P < 0.01$ ). Multivariate Cox regression analysis showed that age, tumor T and N stages, maximum tumor diameter, whether to receive chemotherapy or not and whether to receive postoperative radiotherapy or not were independent prognostic factors (all  $P < 0.01$ ). Subgroup analysis showed except for N0 group ( $P > 0.05$ ), patients with age  $\leq 70$  years and  $> 70$  years, different T stages, lymph node metastasis (N1-N3), maximum tumor diameter  $\leq 5$  cm and  $> 5$  cm, receiving chemotherapy and those who did not receive chemotherapy, could benefit from postoperative adjuvant radiotherapy (all  $P < 0.01$ ). **Conclusion** For advanced gastric signet ring cell carcinoma patients who have received surgery, the prognosis of those with postoperative radiotherapy is better than that without postoperative

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[Key words] signet ring cell carcinoma; stomach neoplasms; adjuvant radiotherapy; survival analysis; SEER database

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胃癌是全世界最常见的恶性肿瘤之一,组织学类型包括腺癌、腺鳞癌、髓样癌、鳞状细胞癌、未分化癌等。印戒细胞癌是一种特殊的腺癌亚型,占原发性胃癌的3.4%~39%,是高度恶性的低分化癌<sup>[1]</sup>。近年来胃癌的总体发病率有所下降,但胃印戒细胞癌的发生率逐步上升<sup>[2]</sup>。胃印戒细胞癌的常规治疗方法为手术切除和术后辅助放化疗,但有研究认为其切除率低、复发率高,且对化疗不敏感<sup>[3]</sup>,预后差。近年有多项研究探讨了胃癌术前与术后放化疗等辅助治疗方案的价值,但术后放疗的临床价值一直存在争议<sup>[4-5]</sup>,且这些研究多针对胃癌进行分析,专门针对印戒细胞癌术后治疗的研究较少。本研究基于监测、流行病学与最终结果(Surveillance, Epidemiology, and End Results; SEER)数据库资料评估术后辅助放疗对中晚期胃印戒细胞癌患者预后的影响,以期为特定胃癌人群的治疗提供一定依据。

## 1 资料和方法

1.1 研究资料 利用SEER\*STAT软件提取SEER数据库中2004—2015年诊断为胃印戒细胞癌(组织学代码ICD-O-3 8490/3)的患者信息。纳入标准:

(1)组织学病理诊断为胃印戒细胞癌;(2)接受以根治为目的的手术治疗;(3)美国癌症联合会(American Joint Committee on Cancer, AJCC)第6版TNM分期为Ⅱ、Ⅲ、Ⅳ期。排除标准:(1)随访信息缺失;(2)肿瘤分级、分期相关信息未知或缺失;(3)多原发癌;(4)确诊时合并远处转移。最终筛选到1 694例患者,其中术后未放疗组907例、术后放疗组787例。记录患者的诊断年份、性别、年龄、种族、婚姻状况、病理分级、AJCC TNM分期、肿瘤原发部位、肿瘤最大径、是否接受化疗等信息。

1.2 统计学处理 应用SPSS 25.0软件进行统计学分析。呈正态分布的计量资料以 $\bar{x} \pm s$ 表示,呈偏态分布的计量资料以中位数(范围或95% CI)表示;

计数资料以例数和百分数表示,组间比较采用 $\chi^2$ 检验。采用Kaplan-Meier法绘制生存曲线。采用log-rank检验进行单因素分析,并将差异有统计学意义的变量纳入多因素Cox回归模型进一步研究独立的预后因素,并进行亚组分析。检验水准( $\alpha$ )为0.05。

## 2 结果

2.1 患者临床病理特征 共1 694例中晚期胃印戒细胞癌患者入组,907例术后未放疗组中男462例、女445例,年龄为65(18~85)岁;787例术后放疗组中男411例、女376例,年龄为58(22~85)岁。两组患者的性别、病理分级、T分期、肿瘤原发部位及肿瘤最大径差异均无统计学意义( $P$ 均 $>0.05$ );两组患者的诊断年份、年龄、种族、婚姻状况、AJCC TNM分期、N分期及是否接受化疗差异均有统计学意义( $P$ 均 $<0.05$ ),其中诊断年份较早的患者较多采用术后放疗,术后放疗组中年龄 $\leq 70$ 岁、黑色人种及其他种族、已婚及分居者、AJCC TNM分期Ⅲ期、N分期1~2期、术后进行化疗的患者比例均高于术后未放疗组。见表1。

2.2 中晚期胃印戒细胞癌患者的预后因素 1 694例中晚期胃印戒细胞癌患者的中位总生存时间为20个月(95% CI 18.54~21.46个月),中位肿瘤特异性生存时间为23个月(95% CI 21.13~24.87个月)。Kaplan-Meier生存分析显示,术后放疗组患者的预后较术后未放疗组患者好( $P < 0.05$ )。见图1。

log-rank单因素分析结果显示,年龄、种族、婚姻状况、AJCC TNM分期、T分期、N分期、肿瘤原发部位、肿瘤最大径、是否接受化疗和术后是否接受放疗是中晚期胃印戒细胞癌患者预后的影响因素( $P$ 均 $<0.01$ ),其中年龄 $>70$ 岁、黑色人种、处于分居或丧偶、AJCC TNM分期晚、T分期晚、N分期晚、肿瘤原发部位在胃交搭跨越部、肿瘤最大径 $>5$  cm、未接受化疗和术后未接受放疗的患者预后均较差。见表2。

表1 术后有无放疗的中晚期胃印戒细胞癌患者的临床病理特征

Tab 1 Clinicopathological characteristics of advanced gastric signet ring cell carcinoma patients with or without postoperative radiotherapy (PRT)

Variable	Without PRT N=907	With PRT N=787	$\chi^2$ value	<i>n</i> (%) <i>P</i> value
Year of diagnosis			13.229	0.001
2004-2008	395 (43.6)	395 (50.2)		
2009-2013	359 (39.6)	303 (38.5)		
2014-2015	153 (16.9)	89 (11.3)		
Gender			0.279	0.631
Female	445 (49.1)	376 (47.8)		
Male	462 (50.9)	411 (52.2)		
Age/year			74.614	<0.001
≤70	566 (62.4)	641 (81.4)		
>70	341 (37.6)	146 (18.6)		
Race			8.826	0.012
African American	105 (11.6)	119 (15.1)		
Others <sup>a</sup>	179 (19.7)	180 (22.9)		
Caucasian	623 (68.7)	488 (62.0)		
Marital status			20.526	<0.001
Divorced	76 (8.4)	59 (7.5)		
Married	529 (58.3)	513 (65.2)		
Separated	7 (0.8)	12 (1.5)		
Single	173 (19.1)	145 (18.4)		
Widowed	122 (13.5)	58 (7.4)		
Pathology grade			1.558	0.669
I	0	1 (0.1)		
II	21 (2.3)	15 (1.9)		
III	854 (94.2)	745 (94.7)		
IV	32 (3.5)	26 (3.3)		
AJCC TNM stage			9.056	0.011
II	290 (32.0)	239 (30.4)		
III	375 (41.3)	378 (48.0)		
IV	242 (26.7)	170 (21.6)		
T stage			3.958	0.266
1	5 (0.6)	10 (1.3)		
2	394 (43.4)	359 (45.6)		
3	396 (43.7)	333 (42.3)		
4	112 (12.3)	85 (10.8)		
N stage			13.702	0.003
0	78 (8.6)	51 (6.5)		
1	379 (41.8)	361 (45.9)		
2	280 (30.9)	271 (34.4)		
3	170 (18.7)	104 (13.2)		
Primary tumor location			8.797	0.360
Cardia	114 (12.6)	90 (11.4)		
Fundus of stomach	26 (2.9)	27 (3.4)		
Body of stomach	100 (11.0)	82 (10.4)		
Gastric antrum	254 (28.0)	234 (29.7)		
Pylorus	44 (4.9)	51 (6.5)		
Lesser curvature of stomach	120 (13.2)	114 (14.5)		
Greater curvature of stomach	46 (5.1)	45 (5.7)		
Overlapping lesion of stomach	111 (12.2)	87 (11.1)		
Stomach, NOS	92 (10.1)	57 (7.2)		
Maximum tumor diameter/cm			3.317	0.076
≤5	407 (44.9)	388 (49.3)		
>5	500 (55.1)	399 (50.7)		
Chemotherapy			486.223	<0.001
Without	493 (54.4)	36 (1.6)		
With	414 (45.6)	751 (95.4)		

<sup>a</sup>: Others indicate American Indian/Alaskan native and Asian/Pacific islander. AJCC: American Joint Committee on Cancer; NOS: Not otherwise specified.

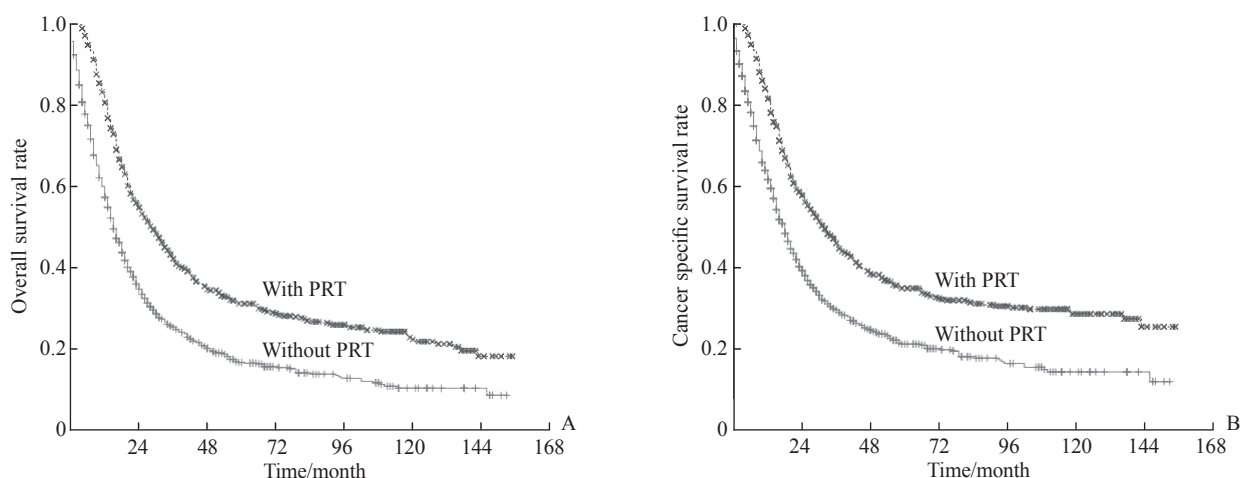


图 1 术后有无放疗中晚期胃印戒细胞癌患者的 Kaplan-Meier 生存曲线

Fig 1 Kaplan-Meier survival curves of advanced gastric signet ring cell carcinoma patients with or without postoperative radiotherapy (PRT)

A: Overall survival curves; B: Cancer specific survival curves.

表 2 中晚期胃印戒细胞癌患者预后的 log-rank 单因素分析

Tab 2 Log-rank univariate analysis of prognosis in patients with advanced gastric signet ring cell carcinoma

Variable	n	OS/month, median (95% CI)	OS rate/%			$\chi^2$ value	P value
			1 year	3 years	5 years		
Year of diagnosis						2.523	0.283
2004-2008	790	20 (17.90, 22.10)	67.2	30.3	21.0		
2009-2013	662	20 (17.69, 22.31)	71.1	34.1	13.6		
2014-2015 <sup>a</sup>	242	20 (15.88, 24.12)	69.4				
Gender						0.237	0.626
Female	821	21 (18.98, 23.02)	69.7	28.3	15.0		
Male	873	20 (18.07, 21.93)	68.5	26.7	15.2		
Age/year						86.122	<0.001
≤70	1 207	24 (21.76, 26.24)	75.6	31.5	17.4		
>70	487	13 (11.15, 14.86)	53.0	17.5	9.5		
Race						11.452	0.003
African American	224	19 (15.76, 22.24)	68.3	25.5	9.8		
Others <sup>b</sup>	359	24 (20.34, 27.67)	73.8	29.8	19.5		
Caucasian	1 111	20 (18.23, 21.77)	67.7	27.1	14.8		
Marital status						25.449	<0.001
Divorced	135	19 (14.30, 23.70)	63.7	19.3	11.1		
Married	1 042	22 (19.92, 24.08)	72.7	30.3	17.1		
Separated	19	14 (1.20, 26.80)	57.9	15.8	5.3		
Single	318	20 (16.21, 23.79)	68.2	26.7	4.5		
Widowed	180	14 (10.11, 17.89)	54.4	19.4	8.9		
Pathology grade						2.037	0.565
I <sup>c</sup>	1	35					
II	36	24 (9.30, 38.70)	72.2	30.6	16.7		
III	1 599	20 (18.50, 21.50)	69.2	27.5	15.1		
IV	58	16 (12.83, 19.17)	63.8	25.9	15.5		
AJCC TNM stage						151.796	<0.001
II	529	39 (32.14, 45.86)	80.5	41.6	24.0		
III	753	20 (18.13, 21.87)	68.5	25.5	13.8		
IV	412	13 (11.61, 14.39)	55.3	12.9	6.1		
T stage						81.818	<0.001
1	15	NR	86.7	40.0	13.3		
2	753	27 (22.81, 31.19)	75.3	36.4	21.5		
3	729	17 (15.37, 18.64)	65.2	20.7	10.2		
4	197	14 (11.92, 16.08)	58.4	17.3	9.1		

续表 2

Variable	n	OS/month, median (95% CI)	OS rate/%			$\chi^2$ value	P value
			1 year	3 years	5 years		
N stage						99.585	<0.001
0	129	31 (21.70, 40.30)	76.0	34.9	17.8		
1	740	27 (23.64, 30.36)	75.4	34.1	20.0		
2	551	18 (16.34, 19.66)	67.2	25.2	13.1		
3	274	13 (11.39, 14.61)	52.6	10.6	4.7		
Primary tumor location						26.754	0.001
Cardia	204	21 (17.46, 24.54)	68.6	25.5	15.7		
Fundus of stomach	53	22 (15.17, 28.84)	71.7	30.2	17.0		
Body of stomach	182	24 (17.33, 30.67)	72.0	27.5	14.3		
Gastric antrum	488	23 (19.82, 26.19)	70.5	29.1	16.8		
Pylorus	95	21 (14.40, 27.60)	73.7	28.4	12.6		
Lesser curvature of stomach	234	21 (17.89, 24.11)	73.1	32.1	17.5		
Greater curvature of stomach	91	25 (16.22, 33.78)	75.8	34.1	17.6		
Overlapping lesion of stomach	198	15 (12.99, 17.01)	58.6	21.7	12.1		
Stomach, NOS	149	18 (14.75, 21.25)	61.1	19.5	9.4		
Maximum tumor diameter/cm						38.22	<0.001
≤5	795	27 (23.29, 30.72)	72.6	34.2	18.7		
>5	899	17 (15.67, 18.33)	66.0	21.5	11.9		
Chemotherapy						150.874	<0.001
Without	529	12 (10.21, 13.79)	49.0	16.4	8.9		
With	1 165	25 (22.31, 27.69)	78.2	32.4	17.9		
Postoperative radiotherapy						95.37	<0.001
Without	907	15 (13.55, 16.45)	58.3	19.6	9.7		
With	787	29 (25.60, 32.40)	81.4	36.5	21.4		

<sup>a</sup>: The patients all didn't reach 3- and 5-year survival; <sup>b</sup>: Others indicate American Indian/Alaskan native and Asian/Pacific islander; <sup>c</sup>: 1 case had no data record of 1-, 3- or 5-year survival rates. AJCC: American Joint Committee on Cancer; NOS: Not otherwise specified; OS: Overall survival; CI: Confidence interval; NR: Not reached.

对单因素分析中差异有统计学意义的变量进行多因素 Cox 回归分析, 结果显示年龄、T 分期和 N 分期、肿瘤最大径、是否接受化疗及术后是否接受放疗是中晚期胃印戒细胞癌患者预后的独立影响因素 ( $P$  均  $<0.01$ )。见表 3。

表 3 中晚期胃印戒细胞癌患者预后的多因素 Cox 回归分析

Variable	$\beta$	SE	Wald	P value	HR (95% CI)
Age	0.399	0.063	40.510	<0.001	1.490 (1.318, 1.685)
T stage	0.362	0.041	76.765	<0.001	1.436 (1.324, 1.556)
N stage	0.311	0.034	83.772	<0.001	1.364 (1.276, 1.458)
Maximum tumor diameter	0.167	0.060	7.786	0.005	1.182 (1.051, 1.329)
Chemotherapy	-0.471	0.070	44.915	<0.001	0.624 (0.544, 0.717)
Postoperative radiotherapy	-0.298	0.067	19.647	<0.001	0.742 (0.650, 0.847)

$\beta$ : Standardized regression coefficient; SE: Standard error; HR: Hazard ratio; CI: Confidence interval.

2.3 亚组分析 为了探讨术后辅助放疗在不同人群中的价值, 以多因素 Cox 回归分析中差异有统计学意义的因素为分组依据进行亚组分析, log-rank 检验结果显示, 除 N0 期亚组 ( $P>0.05$ ) 外, 其余各亚组中术后接受放疗的患者生存时间均优于术后

未接受放疗者 ( $P$  均  $<0.01$ ), 说明除 N0 期亚组 ( $P>0.05$ ) 外, 年龄  $\leq 70$  岁与  $>70$  岁、不同 T 分期、有淋巴结转移 (N1~N3 期)、肿瘤最大径  $\leq 5$  cm 与  $>5$  cm、接受化疗与未接受化疗的患者均能从术后辅助放疗获益。见表 4。

表4 术后接受放疗的中晚期胃印戒细胞癌患者预后的亚组分析

Tab 4 Subgroup analysis of prognosis in advanced gastric signet ring cell carcinoma patients with postoperative radiotherapy (PRT)

Variable	Without PRT		With PRT		$\chi^2$ value	P value
	n	Overall survival	n	Overall survival		
Month, median (95% CI)						
Age/year						
≤70	566	19 (16.80, 21.20)	641	31 (26.81, 35.19)	39.860	<0.001
>70	341	10 (8.41, 11.59)	146	23 (16.94, 29.06)	31.003	<0.001
T stage						
1-2	399	20 (16.89, 23.11)	369	41 (31.80, 50.20)	41.332	<0.001
3	396	14 (12.39, 15.61)	333	23 (19.32, 26.68)	43.694	<0.001
4	112	9 (6.66, 11.34)	85	18 (14.24, 21.76)	10.233	0.001
N stage						
0	78	25 (8.85, 41.15)	51	31 (24.01, 37.99)	1.320	0.251
1-3	829	15 (13.45, 16.55)	736	28 (24.24, 31.76)	99.509	<0.001
Maximum tumor diameter/cm						
≤5	407	18 (15.09, 20.91)	388	37 (31.17, 42.83)	41.433	<0.001
>5	500	14 (12.59, 15.41)	399	21 (18.32, 23.68)	49.712	<0.001
Chemotherapy						
Without	493	10 (8.29, 11.71)	36	21 (8.18, 33.82)	12.334	<0.001
With	414	21 (18.68, 23.32)	751	29 (25.48, 32.52)	12.442	<0.001

CI: Confidence interval

### 3 讨论

目前术后辅助放疗在胃癌治疗中的价值存在争议<sup>[4-5]</sup>。研究表明胃癌对放疗敏感性低,因此长期以来中晚期胃癌的治疗以手术和辅助化疗为主<sup>[6]</sup>。一项有关胃癌D2淋巴结清扫术患者术后辅助放化疗的Ⅲ期临床试验结果显示,对于Ⅲ、Ⅳ期胃癌患者,术后放疗提高了患者的无复发生存率,但对总体生存率的提高并不明显<sup>[7]</sup>。

另一项胃癌临床试验INT0116表明,术后放疗是重要的胃癌辅助治疗手段;该研究随后的随访分析发现,术后辅助同期放化疗能够提高患者的生存率<sup>[8]</sup>。目前对于胃癌中印戒细胞癌这一亚型的辅助放疗方案的研究较少,更多关注辅助化疗。一项纳入272例患者的研究认为,术后接受辅助放化疗的胃印戒细胞癌患者的生存期较接受辅助化疗的患者差<sup>[9]</sup>。然而本研究基于SEER数据库信息的研究结果显示,中晚期的胃印戒细胞癌患者能够从术后辅助放疗中获益。

影响胃印戒细胞癌患者预后的因素尚未达成共识。本研究结果显示,年龄、肿瘤T分期和N分期、肿瘤最大径、是否接受化疗及术后是否接受放疗是胃印戒细胞癌患者的独立预后因素,与

其他研究结果基本一致,即体积大的肿瘤预后较差<sup>[10]</sup>,有较高的淋巴结转移风险及远处转移风险;年龄大的患者表现出较差的预后<sup>[11]</sup>,原因可能是老年人对淋巴结清扫术和辅助治疗的耐受性差,且容易发生对预后有不良影响的并发症。本研究结果显示化疗能改善胃印戒细胞癌患者的预后,与早期的研究结果<sup>[12]</sup>相符,但Li等<sup>[13]</sup>在2020年的一项回顾性研究结果不支持这一观点。

本研究亚组分析结果表明,对于年龄≤70岁与>70岁、不同T分期、有淋巴结转移(N1~N3期)、肿瘤最大径≤5cm与>5cm、接受化疗与未接受化疗的患者,术后辅助放疗均能使患者获益。但术后放疗对于淋巴结转移阴性患者的预后无明显影响,提示N0期患者不能从术后辅助放疗中获益,建议今后临床实践中对于N0期患者可免于术后放疗。

本研究也有一定局限性。由于SEER数据库缺少更具体的临床治疗信息,因此无法获取放疗的具体方案,导致不能对术后放疗技术、放疗靶区范围及剂量进行更详细的研究。此外,作为一项对既往资料的分析研究,一些可能影响结果准确性的混杂因素难以被排除。

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